Birth Outcomes with Depression vs. Antidepressants during Pregnancy

Teri Pearlstein, M.D.

Director, Women's Behavioral Medicine
Women's Medicine Collaborative, a Lifespan Partner
Associate Professor of Psychiatry and Human Behavior
Associate Professor of Medicine
Alpert Medical School of Brown University
Providence, RI

September 21, 2013

Disclosures

- I have the following affiliation(s) and financial interest(s) which should be disclosed:

  Research support from Pfizer, consultant with Ironwood Pharmaceuticals, relationships are not considered directly relevant to the presentation

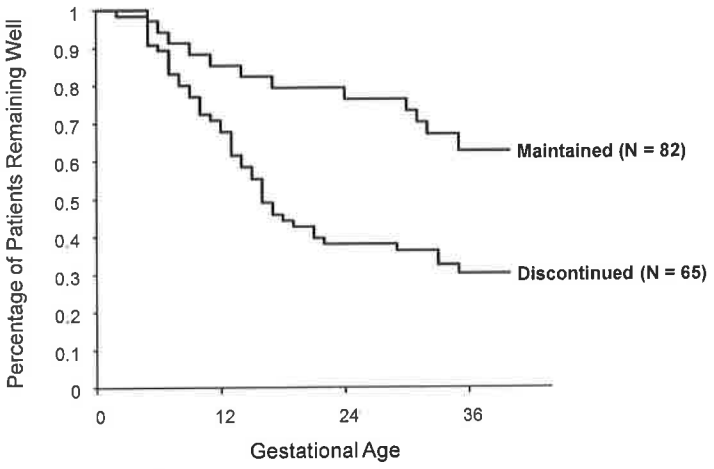
- This presentation does not include discussion of off-label usage of some products or services.

Depression During Pregnancy

- 7-13% prevalence of depression; 1-6% MDD[1,2]
- Risk factors: previous MDD, adolescence, lower SES, poor social support, anxiety, intimate partner violence, recent negative life event, high preconception BMI, diabetes, obstetric risk[3-5]
- Pregnancy not protective, may be a time of risk
- Possible increased suicidal ideation, decreased completion of suicide[6]

[1]Bennett HA et al., Obstet Gynecol 2004;103:698-709; [2]Gavin NI et al., Obstet Gynecol 2005;106:1071-83, [3]Lancaster CA et al., Am J Obstet Gynecol 2010;202:5-14; [4]Melville JL et al., Obstet Gynecol 2010;116:1064-70; [5]Koleva H et al., Arch Womens Ment Health 2011;14:99-105; [6]Newport DJ et al., Arch Womens Ment Health 2007;10:181-7.

Time to Relapse in Patients Who Maintained or Discontinued Antidepressant



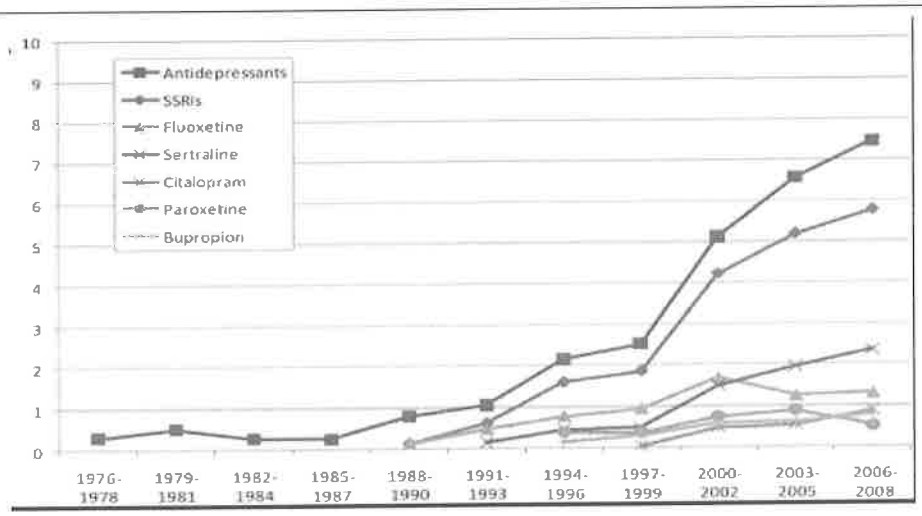
Cohen LS et al., JAMA 2006:295;499-507.

Antidepressant May Not be Protective

- 16% of 778 pregnant women with prior MDD developed MDD during pregnancy
- 75% episodes occurred in 1st trimester
- Maintaining antidepressant not protective
- MDD during pregnancy associated with ≥4 prior episodes or episode in 6 months before conception

Yonkers KA et al., Epidemiology 2011;22:848-54.

First Trimester Antidepressant Use



Mitchell AA et al., Am J Obstet Gynecol 2011;205:51.e1-8.

Effects of Untreated Antenatal Depression, Anxiety and Stress

- Poor self-care, nutrition, health behaviors
- Increased alcohol and drug abuse, smoking
- Increased suicidal ideation
- Spontaneous miscarriage, PTB, LBW, C-section, preeclampsia, lower Apgar scores, placental abruption
- Increased maternal cortisol

Alder J et al., J Matern Fetal Neonatal Med 2007;20:189-209; Beydoun H & Saftlas A, Paediatr Perinat Epidemiol 2008;22:438-66; Li D et al., Human Reprod 2009;24:146-53; Yonkers KA et al., Obstet Gynecol 2009;114:703-13; Zhu P et al., Am J Obstet Gynecol 2010;203:34.e1-8; Davalos DB et al., Arch Womens Ment Health 2012;15:1-14.

Effect of Antenatal Depression on PTB, LBW, and IUGR

Table 2. Effect of Antenatal Depression on Outcomes of PTB, LBW, and IUGR

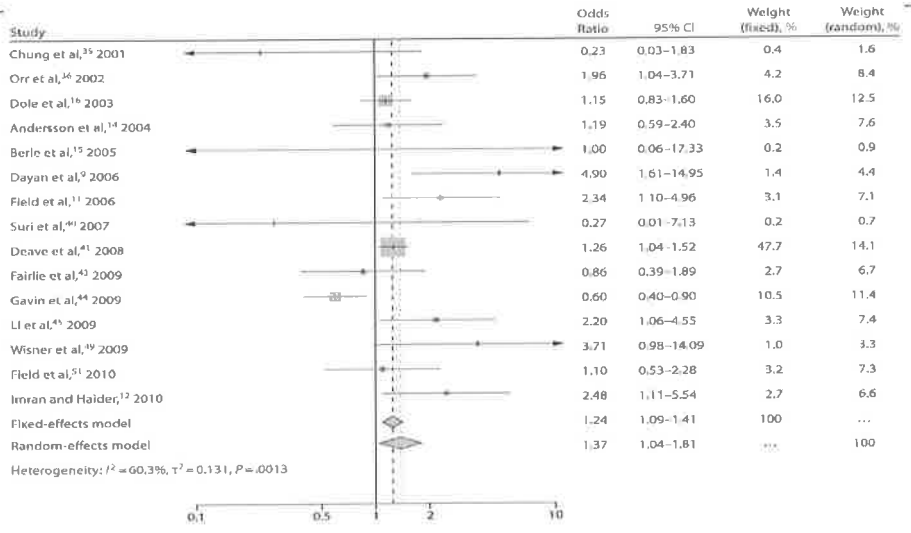
Outcome	No. of Studies	Relative Risk (95% CI)[a]	*P* Value	Heterogeneity Q_W Within	Heterogeneity *P* Value	Heterogeneity Variance Explained, %
PTB	20	1.13 (1.06-1.21)	<.001	49.0_{19}	<.001	61
LBW	11	1.18 (1.07-1.30)	.001	33.8_{10}	<.001	70
IUGR	12	1.03 (0.99-1.08)	.14	22.4_{11}	.02	51

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; LBW, low birth weight; PTB, preterm birth.
[a]Pooled effect size was estimated using the random-effects model.

Grote NK et al., Arch Gen Psychiatry 2010;67:1012-24.

ARCHIVES OF GENERAL PSYCHIATRY

Exposure to Depression in Utero and the Odds Ratio for Premature Delivery: Meta-Analysis Results



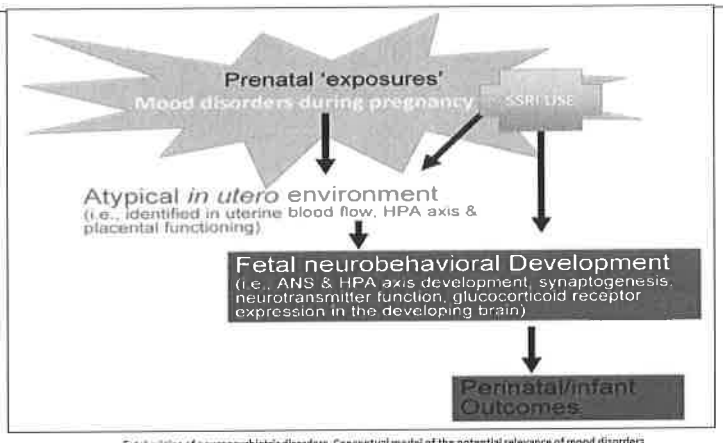
Grigoriadis S et al., J Clin Psychiatry 2013;74:e321-41.

Effects of Untreated Prenatal Depression, Anxiety, and Stress on Child Development

- Right frontal EEG asymmetry, sleep problems
- Developmental delay
- Cognitive impairment
- Internalizing and externalizing behaviors
- ADHD, conduct disorders, antisocial problems
- Increased risk for depression and anxiety disorders
- Altered HPA axis function

Goodman SH & Dimidjian S, Can J Psychiatry 2012;57:530-6; Van den Bergh BR & Marcoen A, Child Dev 2004;75:1085-97; Van den Bergh BR et al., Neurosci Biobehav Rev 2005;29:237-58; Laplante DP et al., Pediatr Res 2004;56:400-10; Hobel CJ et al., Clin Obstet Gynecol 2008;51:333-348; Buss C et al., Stress 2011;14:665-76.

Effects of Mood Disorders and SSRIs on Future Child



Fetal origins of neuropsychiatric disorders. Conceptual model of the potential relevance of mood disorders and pharmacologic treatment during pregnancy for children's neurodevelopmental outcomes.

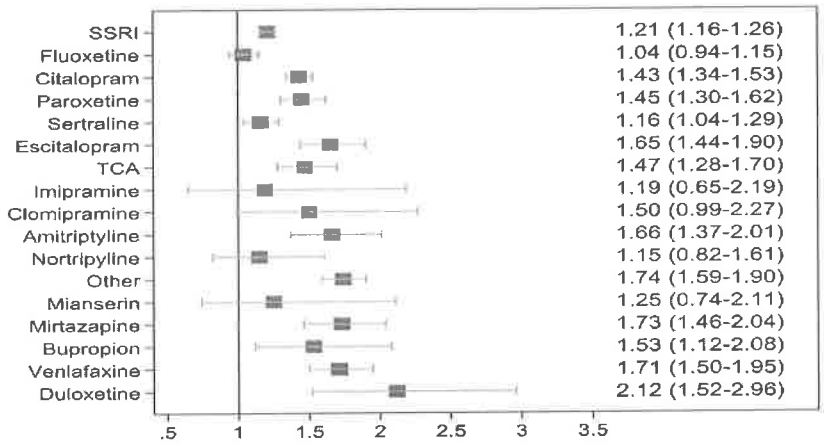
Monk C et al., Pediatr Res 2011;69:3-10R.

Antidepressants and Miscarriage

- Spontaneous miscarriage rate approx. 10%
- 1.45 RR[1] and 1.7 RR[2] in meta-analyses
- 1.63 RR in 937 Motherisk women[3]
- 1.68 RR, paroxetine, venlafaxine higher[4]
- Multiple confounding factors possible including maternal depression[3]

[1]Hemels ME et al., Ann Pharmacother 2005;39:803-9; [2]Rahimi R et al., Reprod Toxicol 2006;22:571-5; [3]Einarson A et al., J Obstet Gynaecol Can 2009;31:452-6; [4]Nakhai-Pour HR et al., CMAJ, 2010;182:1031-7.

Unadjusted RR of Spontaneous Abortion after Exposure to Specific ADs versus no Exposure



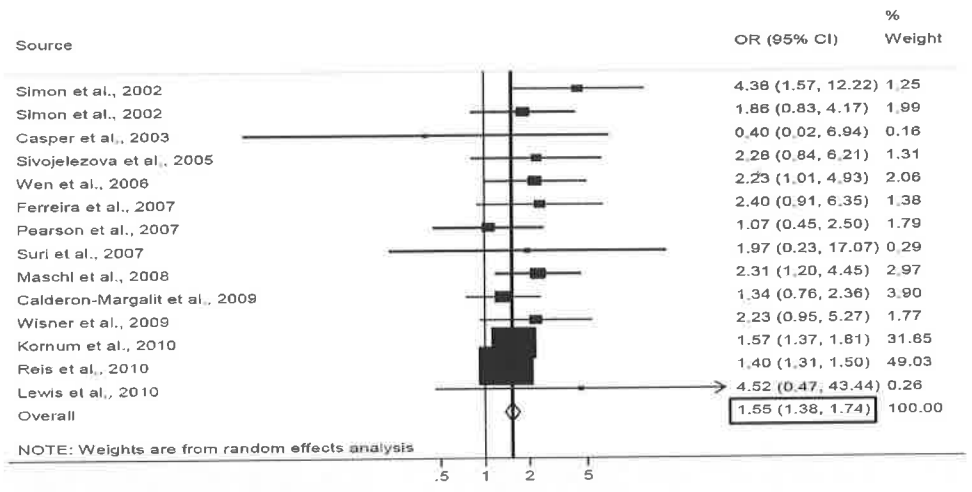
Kjaersgaard MI et al., PLoS One 2013;8:e72095.

Antidepressants and Birth Outcome

- Mixed reports of SSRIs being associated with increased rates of LBW, SGA and PTD[1-6]
- Longer exposure to SSRI and dose may be important, unclear role of timing of SSRI exposure[7,8]

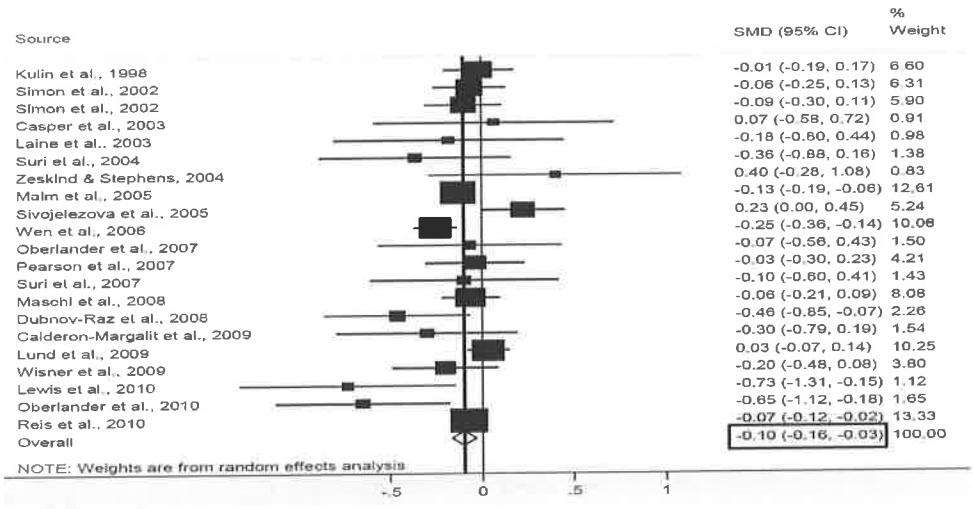
[1]Wisner KL et al., Am J Psychiatry 2009;166:557-66; [2]Einarson A et al., Depress Anxiety 2010;27:35-8; [3]Oberlander TF et al., Arch Gen Psychiatry 2006;63:898-906; [4]Lund N et al., Arch Pediatr Adolesc Med 2009;163:949-54; [5]Yonkers KA et al., Obstet Gynecol 2009;114:703-13; [6]Reis M & Kallen B, Psychol Med 2010;40:1723-33; [7]Calderon-Margalit R et al., Am J Obstet Gynecol 2009;201:579.e1-8; [8]Oberlander T et al., Br J Psychiatry 2008;192:338-43.

Odds Ratios for Premature Delivery Comparing Any Antidepressant Exposure vs. No Exposure



Ross LE et al., JAMA Psychiatry 2013;70:436-43.

Standardized Mean Differences for Birth Weight Between Exposure to Any Antidepressant vs. No Exposure



Ross LE et al., JAMA Psychiatry 2013;70:436-43.

Meta-Analysis Summary

- All of the effects were small in magnitude (approximately 3 days shorter gestational age, 75 grams lower birth weight, and less than half a point on the 1 and 5 minute Apgar scores, with values of the exposed group typically falling within the normal range
- Clinical significance of these risks therefore questionable

Ross LE et al., JAMA Psychiatry 2013;70:436-43.

SSRIs and Preterm Birth

Exposure		Term (n = 2429) No. (%)	Preterm (n = 225) No. (%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	Additionally Adjusted[b] OR (95% CI)
Major Depressive Episode	SRI Use					
Yes	Yes	46 (84)	9 (16)	2.3 (1.11–4.8)	2.14 (0.99–4.6)	1.51 (0.60–3.8)
Yes	No	150 (90)	17 (10)	1.3 (0.79–2.3)	1.19 (0.68–2.1)	0.86 (0.44–1.7)
No	Yes	211 (89)	27 (11)	1.5 (0.98–2.3)	1.62 (1.0–2.5)	1.50 (0.94–2.4)
No	No[c]	2022 (92)	172 (8)	1.0	1.0	1.0

[a]Adjusted for age, education, race, smoking, illicit drug use, and pregnancy history.
[b]Adjusted for age, education, race, smoking, illicit drug use and pregnancy history, number of lifetime hospitalizations, age of depressive onset, number of prior depressive episodes, post-traumatic stress disorder, generalized anxiety disorder, panic disorder in pregnancy, and suicidal thoughts in pregnancy.

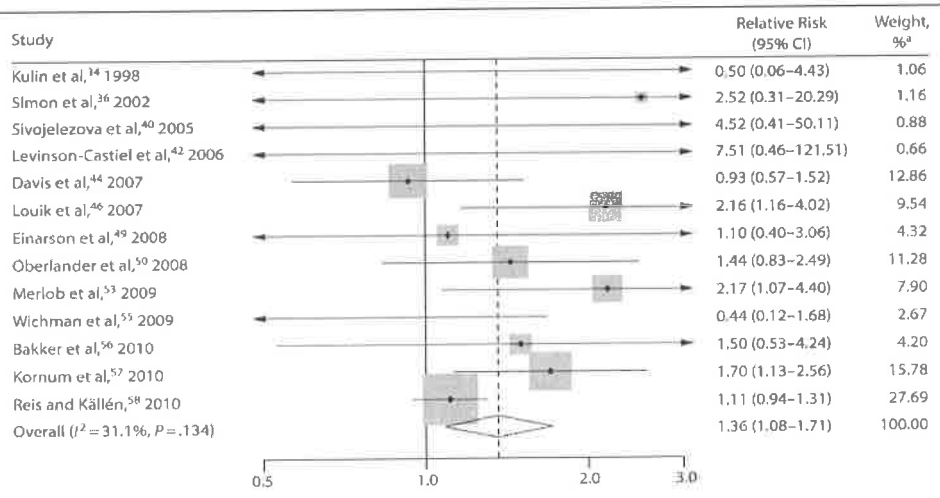
Yonkers KA et al., Epidemiology 2012;23:677-85.

Antidepressants and Congenital Malformations

- Possible small increase in absolute risk of congenital malformations with first trimester SSRI exposure[1]
- Inconsistent defects: septal heart defects, omphalocele, craniosynostosis, anencephaly, ventricular outflow tract heart defects
- Small significant increase in risk of cardiovascular malformations and septal heat defects[2]
- Paroxetine significantly associated with cardiovascular malformations[2,3]

[1]Byatt N et al., Acta Psychiatr Scand 2013;127:94-114; [2]Grigoriadis S et al., J Clin Psychiatry 2013;74:e293-308; Myles, N et al., Aust N Z J Psychiatry 2013;Jun 12[Epub].

Exposure to Antidepressant and Risk of Cardiovascular Malformations



Grigoriadis S et al., J Clin Psychiatry 2013;74:e293-308.

FDA Public Health Advisory – 12/2005

Paroxetine

The Food and Drug Administration (FDA) has determined that exposure to paroxetine in the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiac malformations. At the FDA's request, the manufacturer has changed paroxetine's pregnancy category from C to D and added new data and recommendations to the *Warnings* section of paroxetine's prescribing information.

SSRIs and Congenital Malformations

Outcome	Exposed to any SSRI					No exposure (n=843 797)
	First trimester (n=4183)		Paused during pregnancy (n=808)		p Value*	
	n (%)	OR (95% CI)†	n (%)	OR (95% CI)†		n (%)
Major malformations	208 (4.97)	1.33 (1.16 to 1.53)	36 (4.47)	1.27 (0.91 to 1.78)	0.90	29 703 (3.52)
Congenital malformations of the heart	77 (1.84)	2.01 (1.60 to 2.53)	13 (1.61)	1.85 (1.07 to 3.20)	0.94	7755 (0.92)
Septal defects	49 (1.17)	2.04 (1.53 to 2.72)	11 (1.36)	2.56 (1.41 to 4.64)	0.35	4826 (0.57)
Ventricular septal defects	21 (0.50)	1.62 (1.05 to 2.50)	9 (1.12)	3.74 (1.93 to 7.23)	0.97	2803 (0.33)
Atrial septal defects	34 (0.81)	2.60 (1.84 to 3.68)	6 (0.74)	2.61 (1.17 to 5.84)	0.74	2493 (0.30)
Congenital malformations of the digestive system	13 (0.31)	1.80 (1.04 to 3.12)	1 (0.12)	0.75 (0.11 to 5.35)	0.69	1545 (0.18)
Congenital malformations of the internal urinary system	11 (0.26)	0.84 (0.45 to 1.57)	–	–	–	2333 (0.28)
Congenital malformations of the external genital organs	19 (0.45)	1.55 (0.99 to 2.44)	2 (0.25)	0.89 (0.22 to 3.59)	0.46	2504 (0.30)
Congenital malformations of the limbs	53 (1.27)	0.93 (0.71 to 1.23)	14 (1.74)	1.37 (0.80 to 2.32)	0.18	11 785 (1.40)

Jimenez-Solem E et al., BMJ Open 2012;2(3).e001148.

Persistent Pulmonary Hypertension of the Newborn (PPHN)

- 1-2/1,000 births, 10-20% mortality
- Etiological theories include inhibition of vasodilator nitric oxide, increase in pulmonary smooth muscle proliferation, pulmonary vascular remodeling, genetic polymorphisms[1-4]
- Risk factors include meconium aspiration, cesarean delivery, high BMI, PTD, LGA, diabetes, smoking[4-6]

[1]Chambers CD et al., N Engl J Med 2006;354:579-87; [2]Fornaro E et al., Am J Respir Crit Care Med 2007;176:1035-40; [3]'t Jong G et al., Reprod Toxicol 2012;34:293-7; [4]Occhiogrosso M et al., Am J Psychiatry 2012;169:134-40; [5]Hernandez-Diaz S et al., Pediatrics 2007;120:e272-82; [6]Winovitch KC et al., J Matern Fetal Neonatal Med 2011;24:1398-402.

Risk of PPHN with SSRIs

- 6.1 higher risk with SSRI exposure after week 20[1]
- 2.4 higher risk with use in early pregnancy, 3.6 higher risk with additional use in late pregnancy[2]
- 2.3 risk with use in early pregnancy, 2.56 in later pregnancy, 3.44 throughout pregnancy[3]
- 2.1 higher risk with SSRI exposure after week 20[4]
- No association found in 3 studies[5-7]

[1]Chambers CD et al., N Engl J Med 2006;354:579-87; [2]Kallen B & Olausson PO, Pharmacoepidemiol Drug Saf 2008;17:801-6; [3]Reis M & Kallen B, Psychol Med 2010;40:1723-33; [4]Kieler H et al., BMJ 2012;Jan 12;344:d8012; [5]Andrade SE et al., Pharmacoepidemiol Drug Saf 2009;18:246-52; [6]Wichman CL et al., Mayo Clin Proc 2009;84:23-7; [7]Wilson KL et al., Am J Perinatol 2011;28:19-24.

FDA Alert 7/2006

A recently published case-control study has shown that infants born to mothers who took selective serotonin reuptake inhibitors (SSRIs) after the 20th week of pregnancy were 6 times more likely to have persistent pulmonary hypertension (PPHN) than infants born to mothers who did not take antidepressants during pregnancy. The background risk of a woman giving birth to an infant affected by PPHN in the general population is estimated to be about 1 to 2 infants per 1000 live births. Neonatal PPHN is associated with significant morbidity and mortality.

FDA Drug Safety Communication12/2011

FDA has reviewed the additional new study results and has concluded that, given the conflicting results from different studies, it is premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN. FDA will update the SSRI drug labels to reflect the new data and the conflicting results.

FDA Alert 6/2004

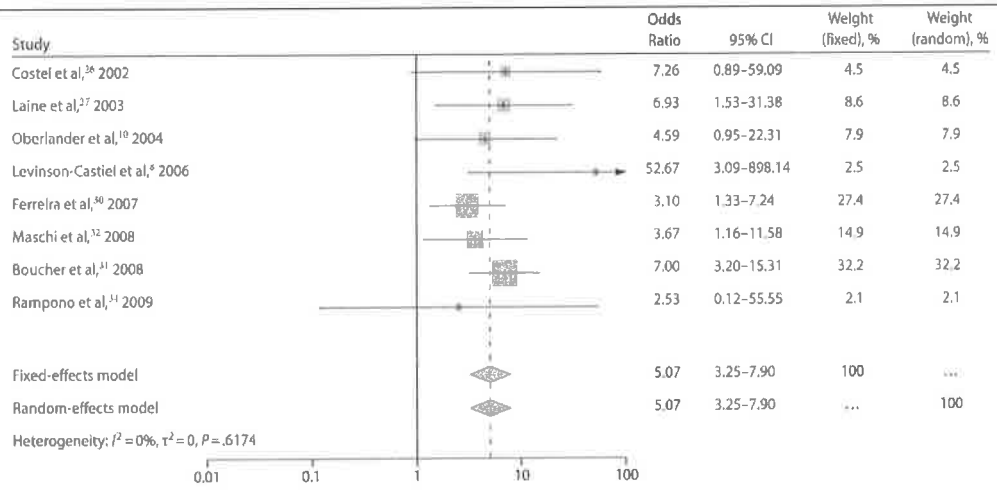
Neonates exposed to SNRIs or SSRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome.

Postnatal Adaptation Syndrome (PNAS)

- May be due to withdrawal from antidepressant or due to increased serotonergic activity
- Occurs in up to 30% newborns
- Symptoms transient, observation and supportive treatment
- Reported with late third trimester exposure to all antidepressants, particularly venlafaxine, paroxetine and fluoxetine, case reports with duloxetine and mirtazapine

Moses-Kolko EL et al., JAMA 2005;293:2372-83; Sanz EJ et al., Lancet 2005;365:482-7; Nordeng H & Spigset O, Drug Saf 2005;28:565-81; Koren G et al., CMAJ 2005;172:1457-9; Gentile S, Drug Saf 2005;28:137-52; Hallberg P & Sjoblom V, J Clin Psychopharmacol 2005;25:59-73; Levinson-Castiel R et al., Arch Pediatr Adolesc Med 2006;160:173-6.

Risk of PNAS with any Antidepressant



Grigoriadis et al., J Clin Psychiatry 2013;74:e309-20.

Tricyclic Antidepressants

- Increased risk or preeclampsia
- Increased risk of PTB and LBW
- Increased risk of neonatal hypoglycemia, respiratory diagnosis, jaundice and low Apgar score
- Possible increased risk of cardiovascular malformations

Reis M & Kallen B, Psychol Med 2010;40:1723-33; Pariante CM et al., Psychol Med 2011;41:15-7.

Other Potential SSRI Effects

- Gestational Hypertension[1,2] and preeclampsia[3]
- Increased risk of postpartum hemorrhage[4]
- Prolonged QTc Interval in Neonate[5]
- Increased mortality at 1 month[6] and 1 year[7]
- No increase in stillbirth or neonatal mortality at 1 month[8,9] or 1 year[9]

[1]Toh S et al., Am J Psychiatry 2009;166:320-8; [2]De Vera MA & Berard A, Br J Clin Pharmacol 2012;74:362-9; [3]Palmsten K et al., Epidemiology 2013;24:682-91; [4]Palmsten K et al., BMJ 2013;347:f4877; [5]Dubnov-Raz G et al., Pediatrics 2008;122:e.710-5; [6]Ban L et al., PLoS One 2012;7:e43462; [7]Colvin L et al., CNS Drugs 2012;26:e1-14; [8]Jimenez-Solem E et al., Am J Psychiatry 2013,170:299-304; [9]Stephansson O et al. JAMA 2013;309:48-54.

Potential Positive SSRI Effects

- Accelerated infant speech perception[1]
- Mitigated effect of prenatal maternal anxiety on infant P50 auditory sensory gating[2]
- Increased infant readiness to interact at 3 months[3]

[1]Weikum WM et al., PNAS 2012;109:17221-7; [2]Hunter SK et al., Am J Psychiatry 2012:169:616-24; [3]Weikum WM et al., Infant Behav Dev 2013;36:485-93.

Long-Term Effects of Prenatal Exposure to Antidepressants

- Increased risk of autism spectrum disorder[1,2]
- Children ages 3-6 with prenatal exposure to venlafaxine, SSRI, and untreated maternal depression all had lower IQ and more behavioral problems than unexposed[3]
- Untreated prenatal depression, but not prenatal exposure to antidepressants, associated with conduct problems at age 4 or 5[4]
- No increase in externalizing behaviors at age 4 with SSRIs[5]
- Mild motor and attention developmental delays with SSRIs[6]
- **Prenatal and postnatal maternal depression critical variables**[3-5,7]

[1]Rai D et al., BMJ 2013;346:f2059; [2]Croen LA et al., Arch Gen Psychiatry 2011;68:1104-12; [3]Nulman I et al., Am J Psychiatry 2012;169:1165-74; [4]Pedersen LH et al., Acta Psychiatr Scand 2013;127:126-35; [5]Oberlander TF et al. Arch Pediatr Adolesc Med 2007;161:22-9; [6]Pedersen LH et al., Pediatrics 2010;125:e600-8 ; [7]Gentile S & Galbally M, J Affect Disord 2011;128:1-9.

Treatment Guideline

The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists

Kimberly A. Yonkers M.D., Katherine L. Wisner M.D., MS., Donna E. Stewart M.D., FRCPC, Tim F. Oberlander M.D., FRCPC, Diana L. Dell M.D., FACOG, Nada Stotland M.D., M.P.H., Susan Ramin M.D., FACOG, Linda Chaudron M.D., MS., and Charles Lockwood M.D., FACOG

Yonkers KA et al., Obstet Gynecol 2009;114:703-13; Gen Hosp Psychiatry 2009;31:403-13.

Depression during Pregnancy: Summary

- There are established short-term and long-term negative consequences of untreated prenatal depression, anxiety and stress
- Prenatal antidepressant medication exposure is associated with increased SA, PTD, cardiovascular anomalies, PPHN, and transient neonatal symptoms
- Partially effective treatment with antidepressants is double exposure
- DOCUMENT informed consent discussions and decisions